REMARKS

Reconsideration and allowance are respectfully requested.

Claims 10-21 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. The Examiner withdrew claims 1-9 and 22-24 from consideration. Therefore, the withdrawn claims are canceled without prejudice or disclaimer to their future prosecution.

35 U.S.C. 112 – Definiteness

Claims 10-21 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse. In contradiction to the Examiner's contention, the structure of "form I" is known in the art.

US 6,429,210, which was cited by Applicants in their specification, is evidence that form I was known by its specific X-ray diffraction structure. The scientific literature known to the skilled artisan also refers to these polymorphic forms of Clopidogrel bisulfate as form I. For example, WO 2004/020443 refers to the '210 patent for form I and form II of Clopidogrel bisulfate (see page 2, line 14). WO 03/114479 also refers to the '210 patent for form I and form II of Clopidogrel bisulfate (see page 4, line 11). There are many other patents that refer to "form I" as such and it is a well-known fact in the art that form I Clopidogrel bisulfate is a well-defined term and not ambiguous. But solely to advance prosecution, and without acquiescing to this rejection, the polymorphic crystalline "form I" is further defined by reciting its melting point in the claims. As the Examiner notes on page 2 of the Office Action, the latter physical property identifies the chemical.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 112 – Written Description

Claims 10-18 and 21 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. It was further alleged, "The claims contain subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention." Applicants traverse. A representative number of "suitable" solvents are taught in their specification. But solely to advance prosecution, and without acquiescing to this rejection, the term "suitable" is deleted because this limitation is not required for patentability.

Withdrawal of the written description rejection is requested.

35 U.S.C. 112 – Enablement

The Patent Office has the initial burden to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04, and the cases cited therein. It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 USPQ 367, 370 (C.C.P.A. 1971). Specific technical reasons are always required. See M.P.E.P. § 2164.04.

Claims 10-21 were rejected under Section 112, first paragraph, as allegedly failing to comply with the enablement requirement for the making of polymorphic forms. It was further alleged, "The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Applicants traverse because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

The processes taught by Applicants in their specification enables the claimed invention. All the solvents shown in the present examples lead to the formation of form I, and any person skilled in the art can practice the invention using the guidance in Applicants' specification. By contrast, there is no evidence of record that production of form I involves any specific temperature, time, or other reaction conditions. The Examiner's example of the production of polymorphic forms of ammonium nitrate is not probative of the different reaction claimed herein. Thus, if this rejection is maintained, the Examiner

is respectfully requested to provide acceptable evidence or reasoning that is inconsistent with (and contradicts) the teachings in the present specification.

Withdrawal of the enablement rejection is requested.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 10-20 were rejected under Section 102(b) or (e) as allegedly anticipated by Bardore et al. (US 4,847,265), Bousquet et al. (US 6,429,210), Valeriano et al. (US 6,800,769), Lifshitz-Liron et al. (US 7,074,928), or Mukarram et al. (US 7,291,735). Applicants traverse.

The claimed invention requires preparing form I Clopidogrel bisulfate by:

- treating Clopidogrel base (as such or derived from Clopodogrel bisulfate or Clopidogrel camphor sulfonate) with dilute H_2SO_4 in suitable solvents selected from C_6-C_{12} alcohols (as recited in claim 20) and subsequently separating the crystals of form I Clopidogrel bisulfate from the solvent or
- treating Clopidogrel base (as such or derived from Clopidogrel bisulfate or Clopidogrel camphor sulfonate) with concentrated H_2SO_4 in suitable solvents selected from C_6-C_{12} alcohols (as claimed in claim 20) and water, subsequently separating the crystals of form I Clopidogrel bisulfate from the solvent.

Therefore, Applicants' claimed invention requires choosing a suitable solvent (e.g., C_6-C_{12} alcohols) for crystallizing Clopidogrel bisulfate in solution, by reaction of Clopidogrel base (as such or derived from Clopidogrel bisulfate or Clopidogrel camphor sulfonate) with H_2SO_4, in order to obtain form I Clopidogrel bisulfate. Specifically, when Clopidogrel camphor sulfonate is the starting material, the camphor sulfonate salt is first converted to Clopidogrel free base using $NaHCO_3$ as in a suitable solvent such as ethyl

acetate, dichioromethane, dichioroethane, chloroform, or a mixture thereof and the base is then taken in a C_6-C_{12} alcohol, treated with H_2SO_4, and crystallized.

The '265 patent (column 6, lines 47-64, as cited by the Examiner) discloses the preparation of methyl α-5(4,5,6,7-tetrahydro(3,2c)thienopyridyl) (2-chlorophenyl)-acetate by the addition of concentrated sulphuric acid dropwise in dichloromethane solvent. By contrast, Applicants disclose preparation of form I (+)-(5) Clopidogrel bisulfate from Clopidogrel base in a different manner. In the present invention, Clopidogrel base is treated with concentrated sulphuric acid in a mixture of a suitable solvent with water. The solvent used here may be selected from the group consisting of C_6 –C_{12} alcohols which may be linear or branched, primary, secondary, or tertiary alcohols such as hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol , 3-heptanol, octanol, iso-octanol, decanol, and mixtures thereof. Since Applicants use a higher alcohol, which is nowhere mentioned in the '265 patent, the claimed process is novel.

The '210 patent (column 6, lines 44-60, as cited by the Examiner) explains the formation of form I Clopidogrel hydrogen sulfate from Clopidogrel camphorsulfate. The process involves addition of Clopidogrel camphorsulfate in dichloromethane solvent and basified by potassium carbonate solution in deionized water. The organic layer was separated and concentrated in vacuum. Acetone was added into the concentrate, and the mixture filtered through 1 to 0.1 micron pores. Then 80% sulphuric acid was added at 20°C, solvent was distilled out, and the residue was cooled to 0 to -5°C. Crystals of form I Clopidogrel hydrogen sulfate were obtained. By contrast, Applicants disclose preparation of form I Clopidogrel bisulfate from Clopidogrel camphorsulfate in a different manner. In present invention, Clopidogrel camphorsulfate is stirred in dichloromethane and basified by sodium bicarbonate solution. The organic layer is separated and solvent is distilled off to get Clopidogrel freebase. The Clopidogrel free base is dissolved in a suitable solvent such as C_6 –C_{12} alcohol which may be a linear or branched, primary, secondary, or tertiary alcohol such as hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 3-heptanol, octanol, iso-octanol, decanol, or a mixture thereof. Then addition of sulphuric acid at 10 to 15°C takes place, and the mixture is stirred for 10 hr at 22-25°C and 4 hr at room temperature. The mixture is filtered and washed with methyl tert-

butyl ether and dried at 30-35°C to get crystals of form I Clopidogrel bisulfate. Since Applicants isolate Clopidogrel base then ultimately prepare form I by the addition of a higher alcohol in this embodiment, which is nowhere mentioned in the '210 patent, the claimed process is novel.

Moreover, the '769 patent relates to a stereospecific process for the preparation of (S),4(S),5(S),7(S)-2,7-dialkyl-4-hydroxy-5-amino-8-aryloctanoyl amides. Since this disclosure is irrelevant to Applicants' disclosure, the claimed process is novel.

The '928 patent (columns 19-20 as cited by the Examiner) explains the formation of form I Clopidogrel bisulfate from Clopidogrel hydrogensulfate and Clopidogrel base. The process involves Clopidogrel base dissolved in absolute ethanol and addition of 80% aqueous sulphuric acid. The mixture was heated to reflux temperature for 2 hr, and product was obtained that was stirred for 2 hr with methyl tert-butyl ether at room temperature. By contrast, Applicants disclose preparation of form I Clopidogrel bisulfate from Clopidogrel base in a different manner. In the present invention, Clopidogrel base is dissolved in a suitable solvent like C_6-C_{12} alcohol which may be a linear or branched, primary, secondary, or tertiary alcohol such as a hexanol, 2-hexanol, 3-hexanol, iso-hexanol, heptanol, 3-heptanol, octanol, iso-octanol, decanol, or a mixture thereof. Since Applicants use a higher alcohol in this embodiment, which is nowhere mentioned in the '928 patent, the claimed process is novel.

The '735 patent (column 4 as cited by the Examiner) explains the formation of form I Clopidogrel bisulfate from (+)-(5)-Clopidogrel. Here, (+)-(5)-Clopidogrel was dissolved in ethyl acetate and seeded with form I Clopidogrel bisulfate, concentrated sulphuric acid was added during stirring. By contrast, Applicants disclose preparation of form I Clopidogrel bisulfate from Clopidogrel base in a different manner, wherein Clopidogrel base is dissolved in a suitable solvent like C_6-C_{12} alcohol which may be a linear or branched, primary, secondary, or tertiary alcohol such as a hexanol, 2-hexanol, 3-hexanol, isohexanol, heptanol, 3-heptanol, octanol, iso-octanol, decanol, or a mixture thereof. Since Applicants use a higher alcohol in this embodiment, which is nowhere mentioned in the '735 patent, the claimed process is novel.

Withdrawal of the Section 102 rejections is requested because the cited patents fail to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. At 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. A claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 10-21 were rejected under Section 103(a) as allegedly unpatentable over Bardore et al. (US 4,847,265) or Bousquet et al. (US 6,429,210), Valeriano et al. (US 6,800,769), Lifshitz-Liron et al. (US 7,074,928), or Mukarram et al. (US 7,291,735) in view of Lifshitz-Liron et al. (US 7,074,928) or Mukarram et al. (US 7,291,735). Applicants traverse.

The term "process" is often misinterpreted as the scale-up work by chemists. One of ordinary skill in the art engaged in various aspects of pharmaceutical process

research and developments have a highly refined appreciation for the challenges in process chemistry. The focus of process chemistry is often more challenging. It emphasizes the optimization of a process. A good process should reliably yield product in high purity. Thus, the objective of a process chemist is always to develop a better and more efficient process, with better purity, with enhanced operational simplicity, reducing the number of steps as even altering the sequence of already known steps, overcoming the drawbacks of existing processes, devising moderate reaction conditions, providing a clean product with lesser side products and impurities, providing an optically pure product without any contamination, devising a safer reaction scheme using less hazardous reactants and milder reaction conditions, and so on. This mission represents a tremendous challenge to the synthetic skills of a process chemist as the requirements for progress to the large-scale production. Thus, the present invention is not obvious.

As mentioned above, the patents cited by the Examiner differ from the present invention in substantial manners and they fail to teach the present invention. It is clear that the '265 patent does not teach preparation of form I Clopidogrel hydrogen sulfate. The process disclosed in the cited patent uses dichloromethane as a solvent, whereas the nonobviousness of Applicants' invention involves the use of at least one higher alcohols. In this respect, the other patents nowhere teach the use of higher alcohols for preparation of form I Clopidogrel hydrogen sulfate. Applicants submit that the use of a higher alcohol as solvent is often difficult in other chemical processes. Hence, higher alcohols are usually not used. Therefore, use of a higher alcohol in Applicants' invention cannot be considered as an obvious substitution due to the known aversion of process chemists to using higher alcohols for other processes because of handling, operational, and scale-up problems.

Further, Applicants submit that none of the cited patents provided evidence that it would have been obvious to use a higher alcohol as the solvent for the claimed process (i.e., preparing crystalline Clopidogrel hydrogen sulfate) with a reasonable expectation of success. In the present invention for preparation of crystalline Clopidogrel hydrogen sulfate, surprising and unexpected results were achieved with the use of higher alcohols as the solvent (e.g., C_6-C_{12}). Applicants' invention has led to development of a more

stable, reproducible, rugged, economical, and commercially viable process for preparing crystalline Clopidogrel hydrogen sulfate. Although alcohols have been used in the past for preparing an active pharmaceutical compound, the use of a higher alcohol is not disclosed anywhere for the preparation of a crystalline hydrogen sulfate salt. Due to the well known demerits of using higher alcohols, one of ordinary skill in the art would have been dissuaded from using a higher alcohol solvent in the claimed process. Therefore, the claimed invention is not obvious.

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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